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Editorial Comment

Thrombolysis: Evidence for Infarct Size Reduction*

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Randomized clinical trials have demonstrated improved survival in patients with acute myocardial infarction treated with intravenous thrombolytic therapy (1,2). Beneficial effects on secondary end points such as vessel patency (3), infarct size (4,5) and ventricular function (6,7) have also been shown. Despite many studies in this area, several key issues regarding the mechanisms of the survival benefit and the relations among secondary end points remain unresolved. In some studies, improved survival has not been accompanied by reduced infarct size (8), and other possible benefits of thrombolysis such as limitation of infarct expansion (9) and a reduced potential for lethal arrhythmias (10,11) have been proposed. In this issue of the Journal, Morgan et al. (12) provide important additional data regarding the relations among vessel patency, infarct size and ventricular function, specifically documenting a reduction in infarct size among treated patients with patent infarct-related vessels.

The Tissue Plasminogen Activator: Toronto (TPAT) trial was a randomized, double-blind trial in which 115 patients with acute myocardial infarction presenting within 3.75 h from the onset of symptoms were treated with intravenous recombinant tissue-type plasminogen activator (rt-PA) or placebo (13). Overall, the study showed improved ventricular function after treatment with rt-PA but failed to detect differences in infarct size. The current study is a retrospective analysis of 108 of these patients grouped according to infarct-related vessel patency determined by coronary angiography either early (18 h) or late (10 days) after myocardial infarction. Global and regional wall motion were assessed by radionuclide ventriculography at 3.8 h and again at 9 days. Infarct size was measured by quantitative single photon emission computed thallium (SPECT) scintigraphy on day 8.

The chief aims of the study were to determine the relations among early and late vessel patency and infarct size and ventricular function, and to assess the relation between the latter two end points. The data show that infarct size was considerably smaller in patients with a patent infarct-related vessel at 18 h (group A) than in those with an occluded vessel. Strong trends toward both better global and better regional function were also observed, supporting the conclusion of a relation between patency and infarct size. In contrast, vessel patency in the group studied only late after myocardial infarction (group B) was not related to either infarct size or ventricular function. Presumably this was because the late patency group comprised not only patients with early patency but also patients with late spontaneous reperfusion, in whom decreased infarct size would not be expected.

A general limitation of this study is the relatively small number of patients, and the authors correctly advise caution regarding conclusions based on these data, especially when no differences are reported. A related weakness is the larger proportion of patients with inferior infarction in the group with early patency (72%) compared with that in the group with early nonpatency (45%). On average, irrespective of treatment, patients with inferior myocardial infarction have a smaller infarct and a higher ejection fraction than do patients with anterior myocardial infarction (4). Unfortunately, the greater percent of patients with inferior myocardial infarction in the group with early patency may be a source of bias in the ejection fraction and infarct size results.

Despite these limitations, the study by Morgan et al. (12) provides additional evidence that the most obvious correlate of preserved left ventricular function is the early presence of a patent infarct-related coronary artery. Data from the Thrombolysis in Myocardial Infarction trial (TIMI Phase I [14]) clearly demonstrated that preservation of left ventricular wall motion was achieved only in patients with initially open vessels and in those with sustained reperfusion. In patients who had unsuccessful or late reperfusion or who had reocclusion, ejection fraction either decreased or did not change. Similarly, in the Western Washington trial of intravenous streptokinase (3), ejection fraction did not differ between control patients with or without a patent infarct vessel assessed 10 days after myocardial infarction.

A possible exception to the conclusion by Morgan et al. (12) that late reperfusion is not associated with improved ventricular function may be patients with angiographically visible collateral vessels to the infarct territory in whom even late reperfusion may improve ejection fraction (14). Collateral vessels were not assessed in the current study. In addition, measurements of ventricular function in the present report reflect systolic wall motion at rest. Whether late vessel patency affects diastolic function or contractile performance during exercise is unknown. As in most other studies, the absolute ejection fraction difference was small, which argues in favor of more comprehensive schemes to evaluate the overall effectiveness of thrombolytic therapy (15).

The infarct size data in the current study are concordant with the regional ejection fraction data and reemphasize the

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importance of early patency. The lack of a difference in infarct size when vessel patency is assessed late is consistent with previous reports showing no decrease in infarct size in patients receiving treatment >3 h after symptom onset (4). The Toronto study is noteworthy in that the mean time to treatment with thrombolysis was 3.1 h, thus optimizing the likelihood of demonstrating an effect on infarct size. A possible weakness in the present report is the use of delayed (4 h) thallium images to determine infarct size because image quality and counting statistics are reduced at 4 h. Redistribution images may also underestimate myocardial salvage as determined by metabolic imaging with use of [^{18}F]fluorodeoxyglucose and positron emission tomography (16). Quantitative analysis of rest images acquired immediately after injection may be a better approach to determining infarct size. The use of newer technetium-labeled flow tracers may allow regional blood flow to be evaluated before treatment, thus allowing late assessment of infarct size to be expressed relative to the area at risk (17–20).

Morgan et al. (12) also report unique data relating infarct size to regional function. A close inverse relation between infarct size and regional wall motion was found among patients with initially occluded vessels, but not among patients with initially open vessels, even when patients with reocclusion were excluded from the latter analysis. Potential explanations for the lack of correlation in patients with initially open vessels are numerous and include the effects of myocardial stunning. Other investigators (5,21) have reported stronger correlations between infarct size and ejection fraction when both are measured late (3 to 12 weeks) after myocardial infarction. Another explanation relates to the general limitations of using ventricular wall motion to assess the intrinsic contractile properties of the ventricle, with which infarct size should be more closely related. Wall motion not only reflects intrinsic contractility but also is affected by loading conditions, drugs and the autonomic nervous system, none of which would be expected to influence infarct size determination. Therefore, the lack of correlation between infarct size and wall motion in this small subset of patients, in whom hemodynamics and drugs were not controlled, is not surprising.

Morgan et al. (12) are to be commended for data that provide insight into the mechanisms of benefit of thrombolytic therapy. For each 100 patients treated with intravenous thrombolytic therapy, approximately three to six lives are saved (1,2,22,23). The Tissue Plasminogen Activator: Toronto data are consistent with the hypothesis that early reperfusion of the infarct-related vessel is associated with reduced infarct size and preserved function that prevent death from contractile failure.

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